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14. ABSTRACT

Backgound: The purpose of this study was to determine predictive relationships between combat experience(s) and the preoperative stress response in U.S. military personnel on the day of surgery.
Methods: This was a prospective, descriptive study enrolling active duty military members undergoing elective surgery. Days prior to surgery measures of anxiety, depression, PTSD symptoms, and combat experience(s) were assessed. On the day of surgery, preoperative stress was measured using the Visual Analogue Scale for Stress, Multiple Affect Adjective Checklist-Revised, and salivary alpha-amylase. A sample size of 120 subjects was calculated and a p value < 0.05 was considered significant.
Findings: Results from 119 subjects were included (76 combat exposed; 43 no combat exposure). Regression modeling suggested anxiety, depression, PTSD, and combat exposure explained 21% of negative emotions (dysphoria) on the day of surgery, $R^2 = .213$, adjusted $R^2 = .180$, $F\ (3, 72) = 6.488$, $p < .001$. In addition, trait depression may be the best predictor of increased preoperative stress, $B = 4.834$, $p < .05$, 95% CI = 1.120 – 8.548. Results also indicated combat exposure alone explained 5.5% of preoperative dysphoria, R^2 change = .055, $F(1, 71) = 5.043$, $p < .05$.
Implications for Military Nursing: These findings corroborate anecdotal reports by perianesthesia providers that combat exposure contributes significantly to preoperative stress. Military anesthetists should consider other emotions when caring for combat veterans, particularly since depression may be the best indicator of preoperative stress. Furthermore, this investigation provides additional evidence necessary to support future interventional studies.

15. SUBJECT TERMS

preoperative stress response, PTSD, anxiety, depression

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Abstract

Backgound: The preoperative period is fraught with a numerous stressors that may be perceived as extremely threatening. Anecdotal reports by military anesthetists suggest combat veterans exhibit a heightened stress response preoperatively. No study has explored the preoperative stress response in military members with and without a history of combat exposure. Therefore, the purpose of this study was to determine predictive relationships between combat experience(s) and the preoperative stress response in U.S. military personnel on the day of surgery.
Methods: This was a prospective, descriptive study enrolling active duty military members undergoing elective surgery. Days prior to surgery measures of anxiety, depression, PTSD symptoms, and combat experience(s) were assessed. On the day of surgery, preoperative stress was measured using the Visual Analogue Scale for Stress, Multiple Affect Adjective Checklist-Revised, and salivary alpha-amylase. A sample size of 120 subjects was calculated and a p value < 0.05 was considered significant.
Findings: Results from 119 subjects were included (76 combat exposed; 43 no combat exposure). Regression modeling suggested anxiety, depression, PTSD, and combat exposure explained 21% of negative emotions (dysphoria) on the day of surgery, $R^2 = .213$, adjusted $R^2 = .180$, $F\ (3, 72) = 6.488$, $p < .001$. In addition, trait depression may be the best predictor of increased preoperative stress, $B = 4.834$, $p < .05$, 95% CI = 1.120 – 8.548. Results also indicated combat exposure alone explained 5.5% of preoperative dysphoria, R^2 change = .055, $F(1, 71) = 5.043$, $p < .05$.
Implications for Military Nursing: These findings corroborate anecdotal reports by perianesthesia providers that combat exposure contributes significantly to preoperative stress. Military anesthetists should consider other emotions when caring for combat veterans, particularly since depression may be the best indicator of preoperative stress. Furthermore, this investigation provides additional evidence necessary to support future interventional studies.

TSNRP Research Priorities that Study or Project Addresses

Primary Priority

Force Health Protection:	☐ Fit and ready force ☐ Deploy with and care for the warrior ☐ Care for all entrusted to our care
Nursing Competencies and Practice:	**X** Patient outcomes ☐ Quality and safety ☐ Translate research into practice/evidence-based practice ☐ Clinical excellence ☐ Knowledge management ☐ Education and training
Leadership, Ethics, and Mentoring:	☐ Health policy ☐ Recruitment and retention ☐ Preparing tomorrow's leaders ☐ Care of the caregiver
Other:	☐

Background

The preoperative period is often perceived as an extremely stressful environment associated with increased psychological alterations and magnified physiological disturbances. Current research suggests patients with higher degrees of stress are more likely to suffer adverse perioperative outcomes, such as increased heart rates, greater anesthetic requirements, postoperative anxiety and pain.[1-5] Anecdotal reports by military anesthesia providers characterize combat veterans as appearing more agitated or anxious prior to undergoing surgery and often times require more medications in order attain an anesthetic depth optimal for surgery. In addition, literature suggests military anesthetists perceive other perioperative behaviors, such as postoperative emergence delirium (ED), to be more prevalent and problematic in combat veterans.[6]

To date, only one study has explored perioperative-related phenomena in individuals with a history of combat exposure. McGuire[7] conducted an observational, descriptive study investigating the incidence of postoperative ED in combat veterans following surgery and found state and trait measures of anxiety were most predictive of postoperative ED when controlling for depression and posttraumatic stress disorder (PTSD). However, no study had researched the *pre*operative psychological and physiological stress response in military personnel with and without a history of combat exposure on the day of surgery. Therefore, the purpose of this study was to determine predictive relationships between combat experience(s) and the preoperative psychological and physiological stress response in U.S. military personnel on the day of surgery independent of mental health morbidity (i.e., anxiety, depression, and PTSD). More specifically, this study was designed to (a) determine predictive relationships between combat experiences and the preoperative *psychological* stress response in U.S. military personnel and (b) determine predictive relationships between combat experiences and the preoperative *physiological* stress response in U.S. military personnel. Study hypotheses were (a) a greater number of combat experiences will be predictive of *more negative emotions* preoperatively as measured by the Multiple Affect Adjective Checklist-Revised (MAACL-R) on the day of surgery, (b) a greater number of combat experiences will be predictive of *higher degrees of stress* preoperatively as measured by the visual analogue scale (VAS) for stress, and (c) a greater number of combat experiences will be predictive of *higher salivary alpha-amylase* (SAA) preoperatively on the day of surgery.

Methodology

This was a prospective, descriptive study enrolling 120 healthy active duty men and women scheduled for surgery at Naval Hospital Camp Pendleton (NHCP). Inclusion criteria included: (a) active duty military men and women; (b) ages 18-45; (c) ASA category I or II; (d) scheduled for elective, noncancer-related surgery requiring anesthesia services (e.g., general anesthesia, monitored anesthesia care, regional anesthesia); (e) able to read and understand the consent form; and (f) consent to participate in the study. The exclusion criteria included (a) medications known to interfere with SAA (e.g., beta-blockers), (b) metabolic disorders (e.g., diabetes, thyroid disorders), and (c) autoimmune disorders (e.g., Sjogren's syndrome).

Patients arriving to the Preoperative Teaching Unit (PTU) for preoperative screening days prior to surgery were approached and provided information about the study. If subjects agreed to participate in the study, then informed consent was obtained. Following enrollment, study subjects completed a demographic and deployment history questionnaire, as well as the

Table 1. Reliability and Validity for Study Instruments

Construct	Instrument	Description	Reliability/Validity
Combat Exposure	Walter Reed Army Institute of Research Combat Exposure Scale[9]	Twenty-seven dichotomized questions measuring combat exposure	Cronbach alpha = .85[9]
Anxiety	Patient Health Questionnaire-4[10]	Four questions derived from the two core criteria for depression and anxiety; Likert-type scale (0=not at all to 3=nearly every day)	Internal reliability for both subscales is high (> .81)[10]
Depression			
PTSD	Posttraumatic Stress Disorder Checklist – Military	Seventeen questions measuring PTSD symptomatology; Likert-type rating scale (1=not at all to 5=extremely); score range 17-85[11]	Internal consistency > .90[12]
Dysphoria	Multiple Affect Adjective Checklist-Revised[13]	One hundred thirty-two adjectives measuring anxiety, depression, and hostility; dysphoria = sum of anxiety, depression, and hostility	Reliability (alpha) is strong (r = .77-.91)[13]
Pain	Visual Analogue Scale	Consists of a 100 mm horizontal line with word descriptors at both ends	High reliability (r > .90) and excellent sensitivity[14-16]
Stress			
Sympathetic Nervous System Activity	Salivary alpha-amylase	Noninvasive, indirect measure of sympathetic nervous system activity	High correlation with other stress biomarkers (r = .53 - .81)[17, 18]

Patient Health Questionnaire-4 (PHQ-4) and Posttraumatic Stress Disorder Checklist-Military (PCL-M) (Table 1). In addition, subjects reporting a prior military deployment where they had received imminent danger pay, hardship duty pay, or combat zone tax exclusion benefits completed the Walter Reed Army Institute of Research Combat Exposure Scale (WRAIR-CES).

On the day of surgery, subjects reported to the Same Day Surgery Unit (SDSU) and were met by the study investigator and directed to a private patient room. Subjects were then asked to submit a saliva sample to measure SAA by placing an oral swab between the right upper gum and cheek area next to the second upper molar for 3 minutes. Concurrently, patients were asked to complete the VAS-pain, VAS-stress, and MAACL-R. Following data collection, a nurse met the subject to complete SDSU admission paperwork, then transported the subject to the preoperative holding area (PHA). Upon arrival to the PHA, subjects were placed on a gurney and immediately met by the study investigator. Subjects were asked to submit a second SAA sample while completing the VAS-S and MAACL-R. Next, the anesthesia provider and operating room team met with the study subject to discuss the operative routine and establish intravenous access. Immediately prior to entering the operating room, but prior to administration of anxiolytics or opioids, subjects submitted a third SAA sample and were asked to complete the VAS-S and MAACL-R one last time. All saliva samples were placed in a cooler until transport to the hospital's laboratory department for storage at -20^{o} C as recommended by Salimetrics, LLC.

The Statistical Package for the Social Sciences (version 21.0) was used to analyze data. Study subjects were assigned to one of two study groups based upon whether they had received special combat-related pay; i.e., subjects having received special pay(s) were categorized as combat-exposed (CE) and those without were assigned to the non-combat exposed (NCE) group. Descriptive statistics were conducted to summarize the demographics and examine measures of central tendency. To explore relationships between study groups, categorical variables were analyzed using a Fisher's Exact Test, Likelihood Ratio, and Pearson's chi-square where appropriate and continuous variables were analyzed using an independent sample *t* test. To explore predictive relationships between the independent and dependent variables, multiple regression analyses were conducted. For each analysis, a *P* value of less than .05 was considered significant.

Results

One hundred twenty active duty military personnel scheduled for elective, noncancer-related surgery at NHCP enrolled in the study. Subjects were assigned to either the CE or the NCE group based upon the subject having received "special combat-related pay" during any prior deployment. Combat-related pay also served as the criteria for CE subjects to complete the WRAIR-CES. On the day of surgery, psychological and physiological measures of stress were collected at three time points (TP): (a) SDSU (TP-1), (b) PHA (TP-2), and (c) immediately prior to OR entry (TP-3).

All 120 subjects completed descriptive and psychometric measures on the day of enrollment; however, one subject voluntarily withdrew from the study on the day of surgery stating, "I really don't want to be in the study." Additional missing data resulted from study measures not collected for one subject at TP-1 and for two subjects at TP-2. Furthermore, Salimetrics, LLC reported eight saliva samples lacked sufficient volume necessary for assay. Lastly, no adverse events occurred throughout the study period.

Baseline demographics. Study subjects were predominately young, Caucasian men serving in the U.S. Marine Corps with an infantry-related military occupation. Slightly more than half (54.6%) of the subjects were either married or in committed relationships and all subjects had an education level at or greater than a high school diploma. Participants had on average seven years of military service with 64% of subjects reporting a prior combat-related deployment (i.e., receiving special combat-related pay). Majority of the CE group (n=76) reported deployments to either Afghanistan or Iraq and had on average seven combat-related experiences according to the WRAIR-CES. The NCE group (n=43) included one subject reporting a military deployment; however, this subject denied receiving any special pay.

Group comparisons related to age and years of military service were conducted using independent sample t-tests and results indicated individuals in the CE group were approximately six years older (CE: $M = 29.33$, $SD = 6.54$ years; NCE: $M = 23.65$, $SD = 3.41$ years; $t\ (117) = -6.23$, $p < .001$) and had on average six more years of military service (CE: $M = 9.05$, $SD = 6.21$ years; NCE: $M = 3.33$, $SD = 3.32$ years; $t\ (117) = -6.56$, $p < .001$). The variables branch of service, military job, ethnicity, highest level of education, marital status, tobacco use, type of surgery, mental health disorders, ASA status, and anesthesia plan were analyzed using nonparametric statistics. Of all categorical variables analyzed, marital status was the only variable found to be significantly different between groups; i.e., more subjects in the CE group were married or in committed relationships, χ^2 (3, N = 119) = 20.65, $p < .001$ (Table 2).

Table 2. Group Demographics

Variable *M (SD)* or N (%)	**Combat Exposure** N = 76 (64%)	**No Combat Exposure** N = 43 (36%)	**Total Sample** N=119	***p* Value** (CE vs. No CE)
Age (years)	29.33 (6.54)	23.65 (3.41)	27.28 (6.23)	**.000***
Gender				
Female	2 (2.6%)	6 (14%)	8 (6.7%)	**.025¶**
Male	74 (97.4)	37 (86%)	111 (93.3%)	
Ethnicity				
Native American	-	3 (7%)	3 (2.5%)	
Asian	2 (2.6%)	2 (4.7%)	4 (3.4%)	
Caucasian	52 (68.4%)	26 (60.5%)	78 (65.5%)	.080§
Latino	13 (17.1%)	10 (23.3%)	23 (19.3%)	
African American	7 (9.2%)	2 (4.7%)	9 (7.6%)	
Other	2 (2.6%)	-	2 (1.7)	
Highest Level of Education				
High School or equivalent	28 (36.8%)	21 (48.8%)	49 (41.2%)	
Some college, no degree	33 (43.4%)	14 (32.6%)	47 (39.5%)	
Two-year college degree	4 (5.3%)	1 (2.3%)	5 (4.2%)	.575§
Four-year college degree	8 (10.5%)	6 (14%)	14 (11.8%)	
Masters, doctorate, or professional degree	3 (3.9%)	1 (2.3%)	4 (3.4%)	
Marital Status				
Single, never married	18 (23.7%)	28 (65.1%)	46 (38.7%)	
Married or in a committed relationship	51 (67.1%)	14 (32.6%)	65 (54.6%)	**.000§**
Divorced	6 (7.9%)	1 (2.3%)	7 (5.9%)	
Separated	1 (1.3%)	-	1 (.8%)	
Mental Health Disorder(s)				
None	65 (85.5%)	42 (97.7%)	107 (89.9%)	
Anxiety	2 (2.6%)	-	2 (1.7%)	
Depression	1 (1.3%)	-	1 (.8%)	.158§
PTSD	6 (7.9%)	1 (2.3%)	7 (5.9%)	
PTSD & Depression	2 (2.6%)	-	2 (1.7%)	

**t* test; ¶Fisher's Exact Test; §Likelihood ratio

Day of Enrollment

Psychological stress measures. A subjective measure of day-to-day stress using the VAS-stress was assessed in both groups on the day of enrollment. Results indicated the NCE group reported slightly less stress as compared to the CE group, CE: $M = 48.87$, $SD = 18.16$; NCE: $M = 47.49$, $SD = 19.18$, $t\ (117) = -.39$, $p = .697$. Trait anxiety and trait depression were also measured on the day of enrollment using the PHQ-4 questionnaire. PHQ-4 mean values revealed both study groups experienced low symptom burden, CE: $M = 2.78$, $SD = 2.71$; NCE: $M = 2.65$, $SD = 2.81$, $t\ (117) = -.24$, $p = .812$. Group mean values using the PHQ-4's two subscales (GAD-2 and PHQ-2) were also compared, although no significant differences were identified, GAD-2: $t\ (117) = -.11$, $p = .910$; PHQ-2: $t\ (117) = -.23$, $p = .823$ (Figure 1 & Table 3).

Cutoff values for each subscale on the PHQ-4 were also used to dichotomize the two scales into *high* trait anxiety (GAD-2 score of 3 or greater) and *high* trait depression (PHQ-2 score of 3 or greater). This resulted in approximately 16% (n = 12) of the CE group and 26% (n = 11) of the NCE group exhibiting *high* trait anxiety, and approximately 22% (n = 17) of CE group and 26% (n = 12) of NCE group respondents displaying *high* trait depression. Group comparisons using a chi-square test for independence indicated no significant relationships between *high* trait anxiety, *high* trait depression, and group assignment, *high* trait anxiety: χ^2 (1, N = 119) = 1.12, $p = .290$); *high* trait depression: χ^2 (1, N = 119) = 1.12, $p = .650$ (Table 3).

Figure 1. Trait Anxiety and Depression Mean Values

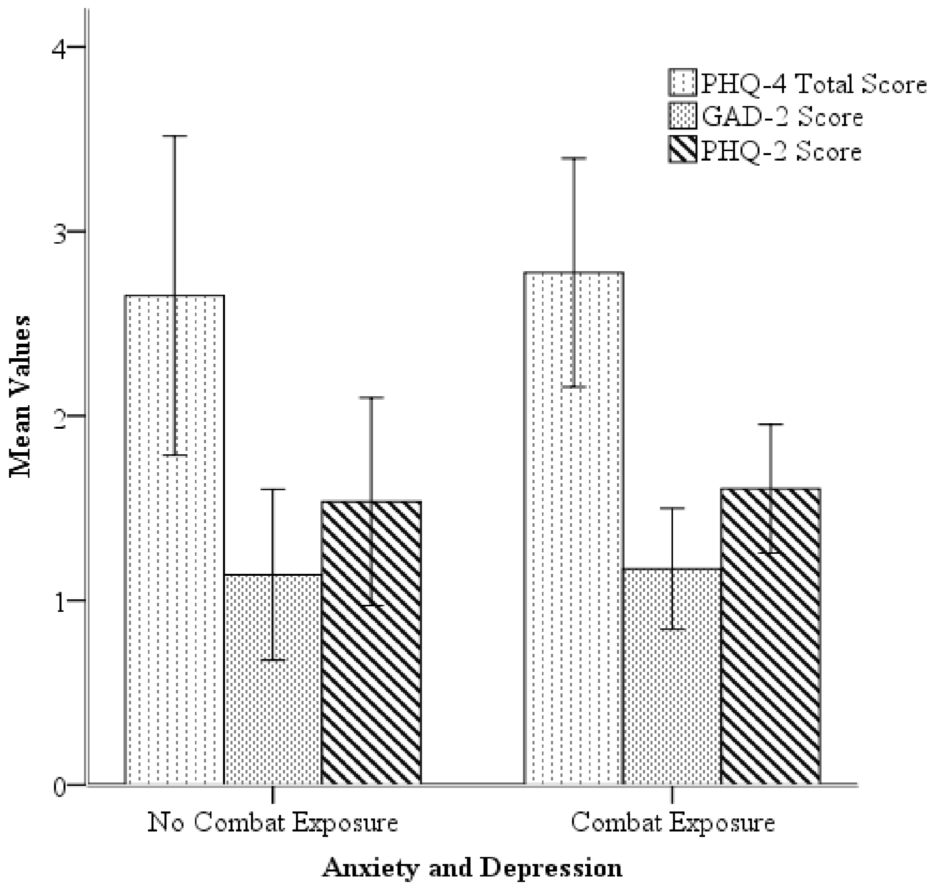


Table 3. Psychological and Physiological Measures

Variable *M (SD)* or N (%)	**Combat Exposure** N = 76 (64%)	**No Combat Exposure** N = 43 (36%)	**Total Sample** N=119	***p* Value** (CE vs. No CE)
VAS-stress over last 6 months	48.87 (18.16)	47.49 (19.18)	48.37 (18.47)	.697*
GAD-2 score	1.17 (1.44)	1.14 (1.51)	1.16 (1.46)	.910*
PHQ-2 score	1.61 (1.52)	1.53 (1.83)	1.58 (1.63)	.823*
PHQ-4 total score	2.78 (2.71)	2.65 (2.81)	2.73 (2.74)	.812*
High GAD-2 Score				
Score < 3	64 (84.2%)	32 (74.4%)	96 (80.7%)	.290±
Score 3 or greater	12 (15.8%)	11 (25.6%)	23 (19.3%)	
High PHQ-2 Score				
Score < 3	59 (77.6%)	31 (72.1%)	90 (75.6%)	.650 ±
Score 3 or greater	17 (22.4%)	12 (27.9%)	29 (24.4%)	
PCL-M total score	29.89 (12.23)	24.91 (9.73)	28.09 (11.60)	**.024***
High PCL-M Score				
Score < 50	68 (89.5%)	42 (97.7%)	110 (92.4%)	.154¶
Score 50 or greater	8 (10.5%)	1 (2.3%)	9 (7.6%)	
WRAIR-CES total score	7.11 (5.80)	-	-	
MAACL-R dysphoria – TP-1	43.00 (5.96)	43.16 (6.73)	43.06 (6.22)	.892*
MAACL-R dysphoria – TP-2	43.80 (6.57)	43.50 (7.64)	43.69 (6.94)	.824*
MAACL-R dysphoria – TP-3	43.36 (6.88)	43.00 (5.90)	43.23 (6.52)	.776*
MAACL-R *mean* dysphoria	43.38 (5.80)	43.22 (5.74)	43.32 (5.76)	.886*
MAACL-R *peak* dysphoria	46.11 (6.16)	46.40 (7.43)	46.21 (7.23)	.834*
VAS-stress – TP-1	32.64 (19.22)	34.49 (21.18)	33.31 (19.89)	.629*
VAS-stress – TP-2	32.87 (19.37)	36.57 (22.52)	34.20 (20.54)	.352*
VAS-stress – TP-3	35.70 (20.10)	36.79 (22.68)	36.09 (20.98)	.786*
VAS-Stress *Mean* Value	33.84 (18.07)	36.22 (20.21)	34.70 (18.82)	.510*
VAS-Stress *Peak* Value	40.88 (20.68)	44.49 (23.70)	42.18 (21.79)	.388*

**t* test; ¶Fisher's Exact Test; §Likelihood ratio

An independent samples t-test comparing group PCL-M mean values indicated CE subjects reported significantly more PTSD-related symptoms, CE: $M = 29.89$, $SD = 12.23$; NCE: $M = 24.91$, $SD = 9.73$, $t\,(117) = -2.293$, $p < .05$. A cutoff value of 50 or greater on the PCL-M was used to dichotomize the variable into *high* PTSD symptoms (PCL-M score of 50 or greater)

Table 3 cont.

Variable *M (SD)* or N (%)	Combat Exposure N = 76 (64%)	No Combat Exposure N = 43 (36%)	Total Sample N=119	*p* Value (CE vs. No CE)
SAA – TP-1	1.01 (.622)	1.15 (.60)	1.06 (.62)	.209*
SAA – TP-2	1.01 (.82)	1.23 (.71)	1.09 (.78)	.150*
SAA – TP-3	1.01 (.83)	1.16 (.58)	1.06 (.75)	.308*
SAA AUC_G	2.13 (1.28)	2.45 (1.08)	2.25 (1.21)	.187*
SAA *mean* increase value	0.08 (.46)	0.05 (.40)	.07 (.43)	.766*
SAA *peak* value	1.30 (.61)	1.49 (.49)	1.37 (.58)	.081*

**t* test

or *low* PTSD symptoms (PCL-M of 49 or less). This particular coding resulted in 8, or 11%, of CE subjects and 1 NCE subject exhibiting *high* PTSD symptomatology; however, no significant difference between groups was found, Fisher's exact test, $p = .15$. Almost half of the subjects (44%) exhibiting *high* PTSD symptoms reported a history of diagnosed PTSD, while 33% had a prior diagnosis of depression (Table 3).

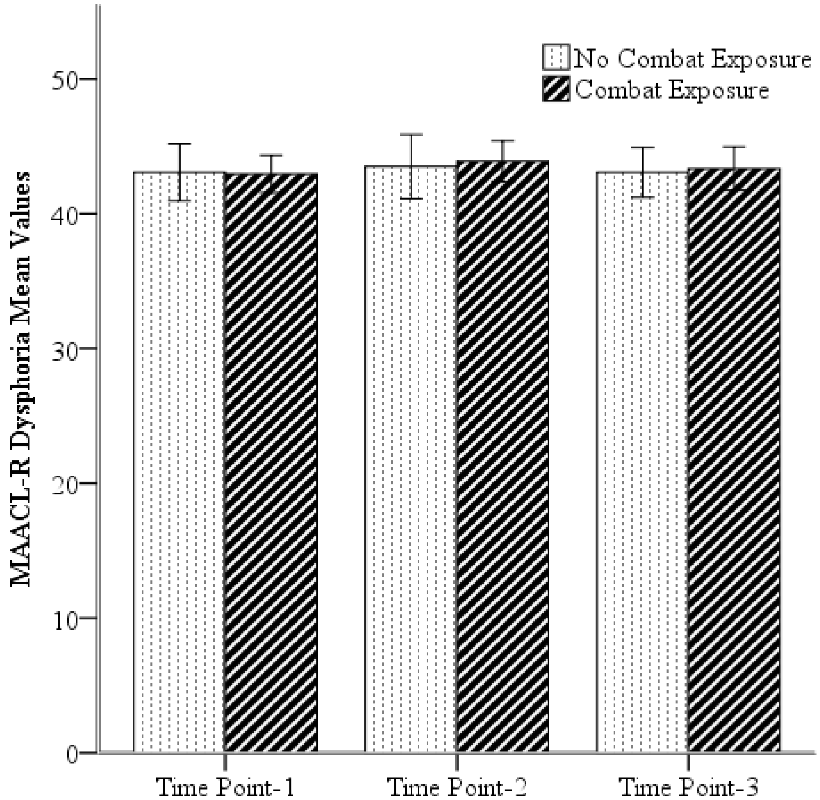
Day of Surgery

Psychological stress measures. On the day of surgery, preoperative psychological stress was measured using the MAACL-R questionnaire. Each MAACL-R questionnaire was analyzed and returned to the study investigator by EdITS, then raw scores were converted to t-scores using a mean value of 50 with a standard deviation of 10.[13] Two outcome variables using MAACL-R dysphoria t-scores were computed: MAACL-R *mean* dysphoria values (mean value from all three TP's) and MAACL-R *peak* dysphoria values (highest dysphoria value among all three TP's). To explore relationships between MAACL-R *mean* dysphoria values and predictor variables, a standard multiple regression analysis was completed. In addition, a stepwise regression with backward elimination was conducted to determine which variable(s) was most predictive of MAACL-R *peak* dysphoria values.

MAACL-R dysphoria values for all subjects (N=119) were below 44, indicating minimal emotional distress; however, four subjects experienced moderate emotional distress (MAACL-R dysphoria t-score > 65). MAACL-R dysphoria values in both groups were highest at TP-2 (Figure 2). Independent samples t-tests comparing group MAACL-R *mean* and *peak* dysphoria values at each TP were conducted; however, no significant differences were found, *mean* values (CE: $M = 43.38$, $SD = 5.80$; NCE: $M = 43.22$, $SD = 5.74$, $t\,(117) = -.144$, $p = .886$) and *peak* values (CE: $M = 46.11$, $SD = 6.16$; NCE: $M = 46.40$, $SD = 7.43$, $t\,(117) = .209$, $p = .834$) (Table 3).

Preoperative psychological stress on the day of surgery was also measured using VAS-stress, from which two VAS-stress values were obtained: VAS-S *mean* values (mean value from all three TP's) and VAS-stress *peak* values (highest VAS-stress score among all three TP's). In order to explore relationships between VAS-stress *mean* values and predictor variables, a standard multiple regression analysis was conducted. Also, a stepwise regression analysis with backward deletion was conducted to determine which variable(s) was most predictive of VAS-stress *peak* values.

Figure 2. MAACL-R Dysphoria Mean Values



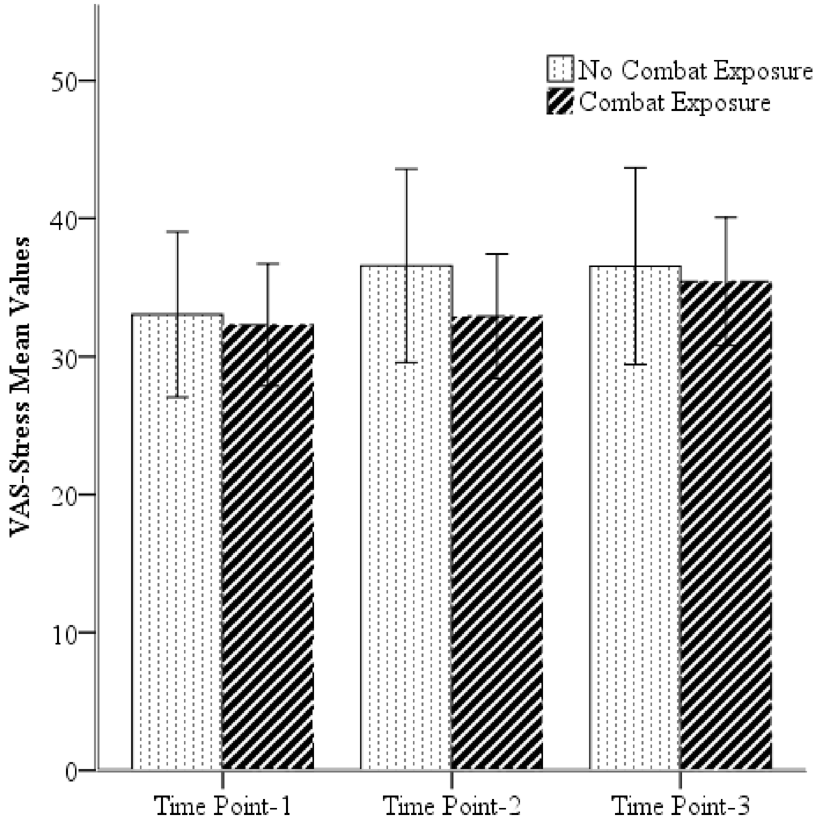
The VAS-stress *mean* values progressively increased in both groups as subjects progressed from TP-1 to TP-3. The NCE group reported slightly more subjective stress across all three TP's; however, there was no significant difference between groups (Figure 3 and Table 3). Group comparisons using independent sample t tests were conducted using VAS-stress *mean* and *peak* values; however, no significant differences were identified, VAS-stress *mean* value: t (117) = .67, p = .510; VAS-stress *peak* value: t (117) = .87, p = .388 (Table 3).

Physiological stress measures. The physiological stress response on the day of surgery was assessed using SAA. Following SAA assay by Salimetrics, LLC, logarithmic transformations were completed to correct for inherently skewed data. For hypothesis testing, SAA area under the curve with respect to ground (SAA AUC_G), SAA *mean* increase values, and SAA *peak* values were calculated (Table 3). Note: To ensure consistency with SAA measures reported throughout stress-related literature, the label "SAA *mean* increase value" will be used instead of the previously used "SAA AUC with respect to increase from baseline" (SAA AUC_{INC}).

Mean SAA values were slightly lower in the CE group across all three TP's as compared to the NCE group, although independent sample t tests displayed no significant difference between the two groups (Figure 4). SAA AUC_G was also slightly lower in the CE group (M = 2.13, SD = 1.28) compared to the NCE group (M = 2.45, SD = 1.08); however, no significant difference was found, t (106) = 1.33, p = .187. In addition, SAA *mean* increase values were slightly higher in the CE group (M = 0.08, SD = 0.46) compared to the NCE group (M = 0.05, SD

= 0.40), although no significant difference between groups was identified, t (106) = -.30, p = .766 (Table 3).

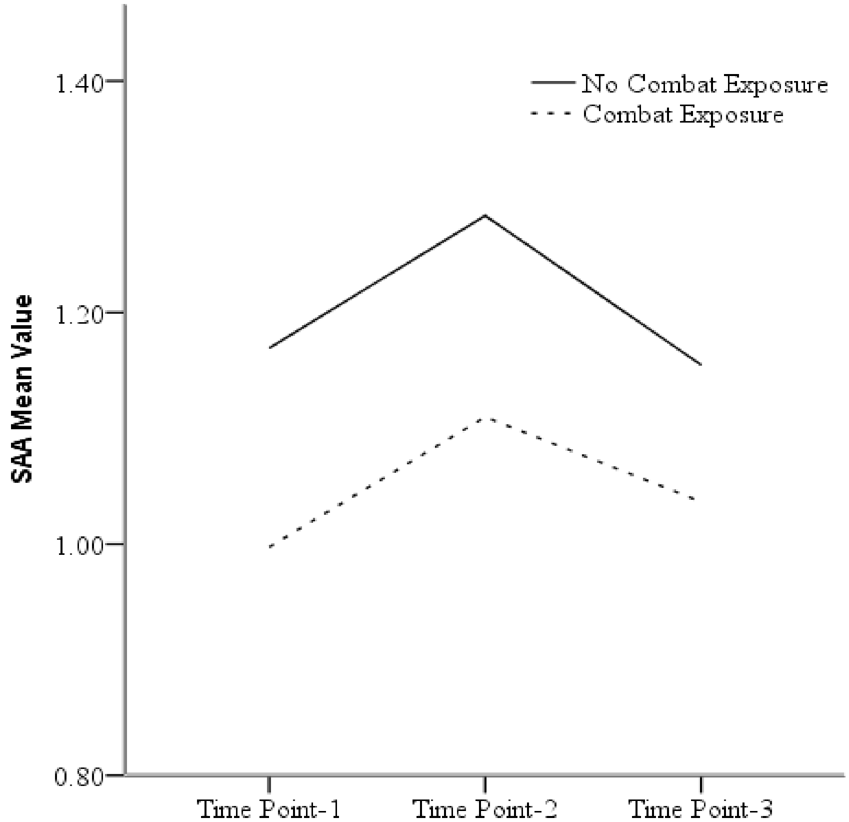
Figure 3. VAS-S Mean Values



Preoperative Psychological Stress Response Analysis

Psychological stress – MAACL-R dysphoria values. The first aim of the study was to determine predictive relationships between combat experiences and the preoperative *psychological* stress response in U.S. military personnel. It was hypothesized that a greater number of combat experiences would be predictive of more negative emotions (dysphoria) on the day of surgery. The first outcome variable used for hypothesis testing was MAACL-R *mean* dysphoria values. A visual inspection of the scatterplots for relations among the predictor variables (WRAIR-CES, PHQ-4, and PCL-M) and criterion variable (MAACL-R *mean* dysphoria values) were completed and all relations were linear. Zero-order correlations were obtained to statistically examine these linear relations. Correlations between the criterion and predictor variables were all statistically significant and displayed small to moderate relationships (Table 4). Subsequently, a standard multiple regression analysis was conducted to determine relationships between the independent variables PHQ-4, PCL-M, and WRAIR-CES and the outcome variable MAACL-R *mean* dysphoria values with all study subjects (N=119) included in the regression model. Examination of collinearity statistics suggested collinearity was not a problem (all tolerance > .2). Results from the regression analysis indicated the overall model significantly predicted MAACL-R *mean* dysphoria values, R^2 = .161, adjusted R^2 = .139, F(3, 115) = 7.356, p < .05. A summary of partial regression coefficients are presented in Table 5, which indicate the predictor variable PHQ-4 was the only variable significantly contributing to the model, $B = .714$, $p < .05$, 95% CI = .212 – 1.216.

Figure 4. SAA Mean Values



Next, a standard multiple regression analysis was conducted by group assignment in order to determine relationships between the independent variables PHQ-4, PCL-M, and WRAIR-CES and the outcome variable MAACL-R *mean* dysphoria values. Examination of collinearity statistics for both groups suggested collinearity was not a problem (all tolerance > .2). In the NCE group, measures of trait anxiety, trait depression, and PTSD symptomatology did not result in significant variance in MAACL-R *mean* dysphoria values, $R^2 = .097$, adjusted $R^2 = .052$, $F(3, 40) = 2.141$, $p = .131$. In the CE group, predictor variables explained approximately 21% of the variance in MAACL-R *mean* dysphoria values, $R^2 = .213$, adjusted $R^2 = .180$, $F(3, 72) = 6.488$, $p < .001$. Additionally, the partial regression coefficient relating anxiety and depression (PHQ-4) to MAACL-R *mean* dysphoria was statistically significant, $B = .760$, $p < .05$, 95% CI = .044 – 1.475 (Table 5).

Further analysis was conducted using cutoff values for each predictor variable in order to determine if higher degrees of anxiety, depression, and PTSD-like symptoms were predictive of increased psychological stress. Accordingly, predictor variables PHQ-4 and PCL-M were removed and replaced with the dichotomized variables *high* trait anxiety (GAD-2 score 3 or greater), *high* trait depression (PHQ-2 score 3 or greater), and *high* PTSD symptomatology (PCL-M score 50 or greater). Correlations between the criterion variable and predictor variables were all statistically significant and displayed small to moderate relationships (Table 4).

Table 4. Predictor and Criterion Variable Correlations

Pearson *r*	WRAIR-CES	PHQ-4	PCL-M	High trait anxiety	High trait depression	High PTSD symptoms
WRAIR-CES	1	.332*	.439**	.324*	.209	.396**
PHQ-4	.332*	1	.701**	-	-	-
PCL-M	.439**	.701**	1	-	-	-
MAACL-R *mean* dysphoria value	.328*	.376**	.305**	.205*	.394**	.200*
MAACL-R *peak* dysphoria value	.331*	.403**	.313**	-	-	-
VAS-stress *mean* value	.702	.258*	.121	-	-	-
VAS-stress *peak* value	.038	.252*	.111	-	-	-
SAA AUC_G	-.200*	-.174	-.143	-	-	-
SAA mean increase	-.109	.120	.058	-	-	-
SAA peak value	-.231*	-.167	-.121	-	-	-

$*p < .05$; $**p < .001$

Table 5. Standard Regression – MAACL-R Mean Dysphoria

Variable	*B*	*SE B*	*β*	*p* Value	CI
<u>All Subjects</u>					
PHQ-4	.714	.254	.339	.006	.212 – 1.216
PCL-M	.004	.064	.008	.952	-.123 – .131
WRAIR-CES	.141	.095	.141	.140	-.047 – .328
Overall R^2 = .161, adjusted R^2 = .139, F (3, 115) = 7.356, p < .001					
<u>NCE Group</u>					
PHQ-4	.586	.377	.287	.128	-.175 – 1.347
PCL-M	.023	.109	.039	.836	-.197 – .242
Overall R^2 = .097, adjusted R^2 = .052, F (3, 40) = 2.141, p = .131					
<u>CE Group</u>					
PHQ-4	.760	.359	.355	.038	.044 – 1.475
PCL-M	-.008	.084	-.016	.928	-.174 – .159
WRAIR-CES	.218	.117	.217	.066	-.015 – .450
Overall R^2 = .213, adjusted R^2 = .180, F (3, 72) = 6.488, p < .001					

Following a standard multiple regression analysis, NCE group results indicated no significant predictive relationships between predictor variables and MAACL-R *mean* dysphoria values, $R^2 = .166$, adjusted $R^2 = .102$, $F(3, 39) = 2.586$, $p = .067$. However, the CE group regression model indicated 23% of the variance in MAACL-R *mean* dysphoria values were explained by the predictor variables, $R^2 = .230$, adjusted $R^2 = .187$, $F(4, 71) = 5.302$, $p < .001$. In addition, examination of regression coefficients indicated WRAIR-CES (combat exposure) and PHQ-2 (*high* trait depression) were statistically significant, $B = .256$, $p < .05$, 95% CI = .029 – .483; $B = 4.834$, $p < .05$, 95% CI = 1.120 – 8.548, respectively (Table 6). Therefore, prior combat exposure and higher degrees of trait depression are more predictive of increased negative emotions on the day of surgery when compared to trait anxiety or PTSD.

A hierarchical multiple regression analysis was conducted to determine the individual contribution of combat exposure to preoperative negative emotions on the day of surgery. In step one of the model, MAACL-R *mean* dysphoria values were entered as the dependent variable and *high* trait anxiety, *high* trait depression, and *high* PTSD symptomatology were entered as predictor variables. As a model, the predictor variables accounted for 17.5% of the variance in MAACL-R *mean* dysphoria values, $R^2 = .175$, adjusted $R^2 = .114$, $F(3,72) = 5.102$, $p < .05$. In step two, the predictor variable WRAIR-CES was entered, resulting in 23% of variance in MAACL-R *mean* dysphoria values being accounted for by the predictor variables, $R^2 = .230$, adjusted $R^2 = .187$, $F(4,71) = 5.302$, $p < .001$. Based upon this model, combat exposure explained an additional 5.5% of the variance in MAACL-R *mean* dysphoria values after controlling for *high* trait anxiety, *high* trait depression, and *high* PTSD symptoms, R^2 change = .055, $F(1, 71) = 5.043$, $p < .05$ (Table 7).

Table 6. Standard Regression – MAACL-R Mean Dysphoria and Cutoff Predictors

	B	*SE B*	*β*	*p* Value	CI
NCE Group					
High GAD-2	-1.834	2.138	-.141	.396	-6.159 – 2.490
High PHQ-2	5.520	2.016	.437	.009	1.443 – 9.597
High PCL-M	5.479	5.829	.146	.353	-6.312 – 17.269
Overall $R^2 = .166$, adjusted $R^2 = .102$, $F(3, 39) = 2.586$, $p = .067$					
CE Group					
WRAIR-CES	.256	.114	.256	.028	.029 – .483
High GAD-2	.431	2.605	.027	.869	-4.764 – 5.625
High PHQ-2	4.834	1.862	.349	.011	1.120 – 8.548
High PCL-M	-.437	2.740	-.023	.874	-5.900 – 5.027
Overall $R^2 = .230$, adjusted $R^2 = .187$, $F(4, 71) = 5.302$, $p < .001$					

An analysis using MAACL-R *peak* dysphoria values was conducted to explore which independent variable (WRAIR-CES, PHQ-4, and/or PCL-M) best predicted MAACL-R *peak* dysphoria. Accordingly, a stepwise regression analysis using backward deletion was conducted with all subjects (N=119) included in the model. A visual inspection of the scatterplots for relations among the dependent and predictor variables was completed and indicated all relations were linear. Zero-order correlations were obtained to examine these linear relationships and

Table 7. Hierarchical Regression – MAACL-R Mean Dysphoria in CE Group

	B	*SE B*	*β*	*p* Value	CI
Step 1					
High GAD-2	.845	2.670	.053	.752	-4.478 – 6.169
High PHQ-2	4.847	1.914	.350	.014	1.032 – 8.663
High PCL-M	1.123	2.724	.060	.681	-4.307 – 6.553
Overall $R^2 = .175$, adjusted $R^2 = .114$, $F(3, 72) = 5.102$, $p < .05$					
Step 2					
High GAD-2	.431	2.605	.027	.869	-4.764 – 5.625
High PHQ-2	4.834	1.862	.349	.011	1.120 – 8.548
High PCL-M	-.437	2.740	-.023	.874	-5.900 – 5.027
WRAIR-CES	.256	.114	.256	.028	.029 – .483
Overall $R^2 = .230$, adjusted $R^2 = .187$, $F(4,71) = 5.302$, $p < .001$					
R^2 change = .055, $F(1, 71) = 5.043$, $p < .05$					

correlations between the dependent and predictor variables were moderate and statistically significant (Table 4). The overall regression model indicated approximately 17% of the variance in MAACL-R *peak* dysphoria values were explained by the predictor variables, $R^2 = .174$, adjusted $R^2 = .153$, $F(3, 115) = 8.099$, $p < .001$. The partial regression coefficient relating PHQ-4 to MAACL-R *peak* dysphoria was statistically significant, $B = .995$, $p < .05$, 95% CI = .369 – 1.621. After criterion for backward regression was met (probability of F-to-remove ≥ .01), the second model removed PCL-M as a predictor and retained PHQ-4 and WRAIR-CES, $R^2 = .174$, adjusted $R^2 = .160$, $F(2, 115) = 12.255$, $p < .001$. Of the two predictor variables in this model, PHQ-4 was statistically significant, $B = .996$, $p < .001$, 95% CI = .543 – 1.449. A third model removed WRAIR-CES as a predictor, $R^2 = .174$, adjusted $R^2 = .155$, $F(1, 117) = 22.631$, $p < .001$. Therefore, trait anxiety and depression (PHQ-4) significantly accounted for 17.4% of the variance in MAACL-R *peak* dysphoria values, $B = 1.064$, $p < .001$, 95% CI = .621 – 1.507 (Table 8).

To analyze changes over time (TP-1 to TP3) using MAACL-R dysphoria values, a Friedman's test was performed on both study groups. No significant difference across the three TP's was found in either group, CE: X^3 (2, $n = 42$) = .867, $p = .648$; NCE: X^3 (2, $n = 74$) = 2.223, $p = .329$) (Table 9).

Psychological stress – VAS-stress values. It was hypothesized a greater number of combat experiences would be predictive of higher degrees of subjective stress on the day of surgery. To explore this hypothesis, a standard multiple regression analysis was conducted using VAS-stress *mean* values as the dependent variable and PHQ-4, PCL-M, and WRAIR-CES as predictor variables. A visual inspection of the scatterplots for relations among independent and dependent variables was completed and indicated all relations were linear. Zero-order correlations were obtained to statistically examine these linear relations and indicated the correlation between PHQ-4 and VAS-stress *mean* values was small, but statistically significant, $r(117) = .258$, $p < .05$. Subjects with higher scores on the PHQ-4 reported more subjective stress. Correlations between VAS-stress *mean* values and the predictor variables WRAIR-CES and PCL-M were not statistically significant, $r(74) = .045$, $p = .702$; $r(117) = .121$, $p = .189$, respectively (Table 4).

Table 8. Backward Regression – MAACL-R Peak Dysphoria in All Subjects

	B	*SE B*	*β*	*p* Value	CI
Model 1					
PHQ-4	.995	.316	.376	.002	.369 – 1.621
PCL-M	.001	.080	.001	.995	-.158 – .159
WRAIR-CES	.143	.118	.114	.228	-.091 – .377
R^2 = .174, adjusted R^2 = .153, F(3, 115) = 8.099, p < .001					
Model 2					
PHQ-4	.996	.229	.377	.000	.543 – 1.449
WRAIR-CES	.143	.109	.114	.190	-.072 – .359
R^2 = .174, adjusted R^2 = .160, F(2, 115) = 12.255, p < .001					
Model 3					
PHQ-4	1.064	.224	.403	.000	.621 – 1.507
R^2 = .174, adjusted R^2 = .155, $F(1, 117) = 22.631$, $p < .001$					

Table 9. Friedman's Test – MAACL-R Dysphoria

		Percentiles		
	n	25th	50th (*Md*)	75th
NCE Group				
TP-1	42	37.00	41.00	47.00
TP-2	42	37.00	40.00	49.25
TP-3	42	37.00	40.50	47.00
CE Group				
TP-1	74	37.00	40.00	47.00
TP-2	74	40.00	44.00	47.00
TP-3	74	37.00	40.00	47.00

A standard multiple regression analysis was conducted with all subjects (N=119) included in the model. This model accounted for approximately 7% of the variance in VAS-stress *mean* values, R^2 = .075, adjusted R^2 = .051, $F(3, 115) = 3.125$, $p < .05$. The regression coefficients are presented in Table 10 and indicate PHQ-4 was the only variable significantly contributing to the model, $B = 2.304$, $p < .05$, 95% CI = .580 – 4.028. Next, a standard multiple regression analysis was conducted on each group; however, no significant relationships between VAS-stress *mean* values and predictor variables were found in either group, CE: R^2 = .085, adjusted R^2 = .047, $F(3, 72) = 2.239$, $p = .091$; NCE: R^2 = .084, adjusted R^2 = .038, $F(2, 40)$ = 1.830, $p = .174$ (Table 10).

A stepwise regression analysis using backward deletion was conducted to explore which independent variable was most predictive of VAS-stress *peak* values. VAS-stress *peak* values were entered into the regression model as the dependent variable and PHQ-4, PCL-M, and WRAIR-CES were entered as predictor variables. Inspection of the scatterplots for relations

Table 10. Standard Regression – VAS-Stress Mean Value

Variable	*B*	*SE B*	*β*	*p* Value	CI
<u>All Subjects</u>					
PHQ-4	2.304	.870	.335	.009	.580 – 4.028
PCL-M	-.154	.220	-.095	.485	-.591 – .282
WRAIR-CES	-.144	.325	-.044	.659	-.788 – .500
Overall R^2 = .075, adjusted R^2 = .051, $F(3, 115) = 3.125$, $p < .05$					
<u>NCE Group</u>					
PHQ-4	2.545	1.336	.354	.064	-.155 – 5.245
PCL-M	-.481	.386	-.232	.220	-1.260 – .299
Overall R^2 = .084, adjusted R^2 = .038, $F(2, 40) = 1.830$, $p = .174$					
<u>CE Group</u>					
PHQ-4	1.941	1.204	.291	.111	-.460 – 4.342
PCL-M	.030	.280	.021	.914	-.528 – .589
WRAIR-CES	-.191	.391	-.061	.627	-.970 – .589
Overall R^2 = .085, adjusted R^2 = .047, $F(3, 72) = 2.239$, $p = .091$					

among independent and dependent variables indicated all relations were linear. There was a small statistically significant correlation between VAS-stress *peak* values and PHQ-4, $r(117) = .252$, p < .05 (Table 4). With all subjects included (N=119), the overall model indicated 7.5% of the variance in VAS-stress *peak* values was explained by the predictor variables, $R^2 = .075$, adjusted $R^2 = .051$, $F(3, 115) = 3.108$, $p < .05$. Partial regression coefficients for this model indicated PHQ-4 was the only variable statistically significant, $B = 2.674$, $p < .05$, 95% CI = .677 – 4.670. After criterion for backward regression was met (probability of F-to-remove ≥ .01), the second model removed WRAIR-CES as a predictor variable and retained PHQ-4 and PCL-M, thus explaining 7.2% of the variance in VAS-stress *peak* values, $R^2 = .072$, adjusted $R^2 = .056$, $F(2, 116) = 4.522$, $p < .05$. In this model, the partial regression coefficient relating PHQ-4 to VAS-stress *peak* values was statistically significant, $B = 2.737$, $p < .05$, 95% CI = .758 – 4.716. A third model removed PCL-M as a predictor variable, indicating the predictor variable PHQ-4 accounted for approximately 6% of the variance in VAS-stress *peak* values, $R^2 = .064$, adjusted $R^2 = .056$, $F(1, 117) = 7.965$, $p < .01$ (Table 11).

A one-way repeated measures ANOVA was conducted to compare VAS-stress values over time (i.e., TP-1 – TP-3). For subjects in the NCE group, there was not a significant difference in VAS-stress values over time, Wilk's Lambda = .935, F (2, 40) = 1.384, $p = .262$, multivariate partial eta squared = .065. Likewise, no significant effect for VAS-stress over time was found in the CE group, Wilk's Lambda = .942, F (2, 72) = 2.223, $p = .116$, multivariate partial eta squared = .058 (Table 12).

Preoperative Physiological Stress Response Analysis

Physiological stress – SAA values. The second aim of the study was to determine predictive relationships between combat experiences and the preoperative *physiological* stress response in U.S. military personnel. It was hypothesized that a greater number of combat

Table 11. Backward Regression – VAS-Stress with All Subjects

	B	*SE B*	*β*	*p* Value	CI
Model 1					
PHQ-4	2.674	1.008	.336	.009	.677 – 4.670
PCL-M	-.189	.255	-.100	.461	-.694 – .317
WRAIR-CES	-.217	.376	-.057	.565	-962 – .529
Overall R^2 = .075, adjusted R^2 = .051, F(3, 115) = 3.108, p < .05					
Model 2					
PHQ-4	2.737	.999	.344	.007	.758 – 4.716
PCL-M	-.244	.236	-.130	.302	-.711 – .222
Overall R^2 = .072, adjusted R^2 = .056, F(2, 116) = 4.522, p < .05					
Model 3					
PHQ-4	2.010	.712	.252	.006	.600 – 3.421
Overall R^2 = .064, adjusted R^2 = .056, $F(1, 117) = 7.965$, $p < .01$					

Table 12. RM-ANOVA VAS-Stress

	n	*M*	*SD*
NCE Group			
TP-1	42	33.05	19.18
TP-2	42	36.57	22.52
TP-3	42	36.55	22.90
CE Group			
TP-1	74	33.30	19.12
TP-2	74	32.92	19.50
TP-3	74	35.43	20.00

experiences would be predictive of higher SAA values as measured by SAA AUC_G and SAA *mean* increase values. In order to test this hypothesis using SAA AUC_G values, a standard multiple regression analysis was conducted and SAA AUC_G was entered as the dependent variable and PHQ-4, PCL-M, and WRAIR-CES were entered as predictor variables. Scatterplots for relations among variables displayed negative, linear relationships. Zero-order correlations between the predictor variables and dependent variable were small and not significant (Table 4). Examination of collinearity statistics suggested that collinearity was not a problem (all tolerance values > 2).

When all subjects (N=119) were included in the analysis, the model indicated no significant predictive relationships between the predictor variables and SAA AUC_G, R^2 = .059, adjusted R^2 = .031, $F(1, 104) = 2.160$, $p = .097$. Next, a standard multiple regression analysis was repeated by group assignment. The NCE group results indicated no predictive relationships between the predictor variables and SAA AUC_G, R^2 = .056, adjusted R^2 = .006, $F(2, 38) = 1.128$, $p = .334$. Likewise, the CE group analysis indicated no significant relationship between the predictor variables and SAA AUC_G, R^2 = .050, adjusted R^2 = .005, $F(3, 63) = 1.107$, p = .353. A summary table of the partial regression coefficients for each model are presented in Table 13.

Table 13. Standard Regression – SAA AUC_G

	B	*SE B*	*β*	*p* Value	CI
<u>All Subjects</u>					
PHQ-4	-.094	.093	-.199	.315	-.280 – .092
PCL-M	.016	.022	.153	.462	-.027 – .059
WRAIR-CES	-.041	.030	-.187	.176	-.102 – .019.
Overall R^2 = .059, adjusted R^2 = .031, $F(1, 104) = 2.160$, p = .097					
<u>NCE Group</u>					
PHQ-4	-.061	.075	-.157	.422	-.212 – .090
PCL-M	-.012	.022	-.108	.580	-.056 – .032
Overall R^2 = .056, adjusted R^2 = .006, $F(2, 38) = 1.128$, p = .334					
<u>CE Group</u>					
PHQ-4	-.094	.093	-.199	.315	-.280 – .092
PCL-M	.016	.022	.153	.462	-.027 – .059
WRAIR-CES	-.041	.030	-.187	.176	-.102 – .019.
Overall R^2 = .050, adjusted R^2 = .005, $F(3, 63) = 1.107$, p = .353					

Next, SAA AUC_G was replaced by the outcome variable SAA *mean* increase values and a standard regression analysis was repeated using the same predictor variables. Collinearity statistics were assessed in both groups indicating collinearity was not a problem (all tolerance > .2). Scatterplots were assessed for relations among the proposed variables and each displayed a linear relationship, although the correlations between variables were small and not significant (Table 4). When considering all subjects in the statistical model, results indicated no significant relationship between the predictor variables and SAA *mean* increase values, R^2 = .022, $F(3, 104)$ = .773, p = .512. The regression model was repeated based upon group assignment and neither model indicated a significant relationship, NCE: R^2 = .008, $F(2, 38)$ = .159, p = .854; CE: R^2 = .054, $F(3, 63) = 1.201$, p = .317. Partial correlation coefficients relating the predictor variables to SAA *mean* increase values are provided in Table 14.

Table 14. Standard Regression – SAA *Mean* Increase

	B	*SE B*	*β*	*p* Value	CI
All Subjects					
PHQ-4	.023	.022	.145	.291	-.020 – .066
PCL-M	.000	.006	-.008	.956	-.011 – .011
WRAIR-CES	-.006	.008	-.085	.430	-.023 – .010
Overall R^2 = .022, $F(3, 104) = .773$, $p = .512$					
NCE Group					
PHQ-4	.004	.028	.030	.879	-.053 – .061
PCL-M	.003	.008	.070	.726	-.014 – .019
Overall R^2 = .008, $F(2, 38) = .159$, $p = .854$					
CE Group					
PHQ-4	.049	.033	.291	.143	-.017 – .115
PCL-M	-.005	.008	-.122	.555	-.020 – .011
WRAIR-CES	-.012	.011	-.152	.269	-.033 – .009
Overall R^2 = .054, $F(3, 63) = 1.201$, $p = .317$					

A stepwise regression using backward deletion was completed to explore which predictor variable was most predictive of an individual's SAA *peak* value. Accordingly, SAA *peak* values were entered as the dependent variable and PHQ-4, PCL-M, and WRAIR-CES were entered as predictor variables. A visual inspection of the scatterplots for relations among trait anxiety and depression, PTSD symptomatology, combat experiences, and SAA *peak* values were linear. Correlations were obtained and WRAIR-CES was the only variable found to significantly correlate with SAA *peak* values, although the relationship was a weak, inverse relationship, $r(74) = -.213$, $p < .05$ (Table 4). This relationship suggests individuals reporting more combat experience will exhibit lower SAA *peak* values and individuals with less combat experience will exhibit higher SAA *peak* values.

With all study subjects included, the overall model significantly predicted SAA *peak* values, $R^2 = .084$, adjusted $R^2 = .060$, $F(3, 115) = 3.502$, $p < .05$. The partial regression coefficient relating WRAIR-CES to SAA *peak* values was statistically significant, $B = -.026$, $p < .05$, 95% CI = -.046 – -.007. After criterion for backward regression was met (probability of F-to-remove ≥ .01), the second model removed the PCL-M as a predictor and retained PHQ-4 and WRAIR-CES, which accounted for 7.7% of the variance in VAS-stress *peak* values, $R^2 = .077$, adjusted $R^2 = .061$, $F(2, 116) = 4.808$, $p < .05$. Of the two predictors variables, WRAIR-CES significantly contributed to the model, $B = -.023$, $p < .05$, 95% CI = -.041 – -.005. A third model removed PHQ-4 as a predictor and retained WRAIR-CES, $R^2 = .064$, adjusted $R^2 = .056$, $F(1, 117) = 7.978$, $p < .01$. In the final model, WRAIR-CES accounted for 6.4% of the variance in SAA stress *peak* values. Partial correlation coefficients relating predictor variables to SAA *peak* values are provided in Table 15.

Table 15. Backward Regression – SAA Peak Values

	B	*SE B*	*β*	*P* value	CI
Model 1					
PHQ-4	-.042	.027	-.198	.119	-.094 – .011
PCL-M	.006	.007	.128	.345	-.007 – .020
WRAIR-CES	-.026	.010	-.262	.009	-.046 – -.007
Overall R^2 = .084, adjusted R^2 = .060, $F(3, 115) = 3.502$, $p < .05$					
Model 2					
PHQ-4	-.024	.019	-.116	.209	-.063 – .014
WRAIR-CES	-.023	.009	-.227	.015	-.041 – -.005
Overall R^2 = .077, adjusted R^2 = .061, $F(2, 116) = 4.808$, $p < .05$					
Model 3					
WRAIR-CES	-.025	.009	-.253	.006	-.043 – -.008
Overall R^2 = .064, adjusted R^2 = .056, $F(1, 117) = 7.978$, $p < .01$					

To determine changes in SAA values over time for both study groups, a Friedman's test was performed since assumptions for repeated measures ANOVA were not met. For both groups, the Friedman's test indicated no significant difference in SAA values over time, NCE: X^3 (2, n=41) = 4.439, $p = .109$; CE: X^3 (2, n=67) = 4.299, $p = .117$ (Table 16).

Table 16. Friedman's Test – SAA values

		Percentiles		
	n	25th	50^{th} (*Md*)	75th
NCE Group				
TP-1	41	.73	1.31	1.55
TP-2	41	.89	1.36	1.74
TP-3	41	.85	1.25	1.56
CE Group				
TP-1	67	.56	.97	1.51
TP-2	67	.66	1.17	1.60
TP-3	67	.66	1.19	1.54

Discussion

This may be the first investigation to explore predictive relationships between combat exposure and the preoperative stress response in military members. In recent years, an interest in postoperative emergence delirium within the military surgical population has emerged; however, no investigation to date has studied the *preoperative* stress response on the day of surgery, particularly in individuals with and without a history of combat exposure. This study is unique in that it measured a variety of combat experiences by utilizing the U.S. Army's Combat Exposure Scale; i.e., WRAIR-CES. In addition, this study enrolled individuals *without* prior combat experience, thus allowing this project to better ascertain the effect of combat exposure upon an individual's preoperative stress response on the day of surgery.

One outcome variable used to measure preoperative psychological stress on the day of surgery was dysphoria. When considering MAACL-R *mean* dysphoria values, results indicated approximately 21% of dysphoria experienced by combat-exposed personnel was related to trait measures of anxiety and depression, combat exposure, and PTSD symptoms. However, trait anxiety and trait depression were the only variables significantly contributing to increased dysphoria on the day of surgery. Similarly, trait measures of anxiety and depression were the only independent variables significantly predicting preoperative *peak* dysphoria values on the day of surgery. The relationships identified in this study between trait measures of anxiety and depression and *mean* and *peak* dysphoria, particularly in combat veterans, are new findings not found in current preoperative stress literature. These findings are meaningful in that they highlight the potential impact day-to-day psychological disorders, such as trait anxiety and/or trait depression, may have upon a combat veteran's perception of the preoperative experience.

Recent literature suggests postoperative ED in military members is increasingly more prevalent and problematic. Furthermore, many military anesthetists presume PTSD as the primary reason for combat veterans experiencing heightened or exacerbated behaviors perioperatively. Wilson[6] reported 78% of U.S. Army anesthetists had cared for patients exhibiting ED-like behaviors and most of these providers perceived PTSD as the primary cause of postoperative ED. However, McGuire[7] collected measures of anxiety, depression, and PTSD symptoms in combat veterans days prior to surgery and found state and trait anxiety were most predictive of postoperative ED, not PTSD.[2] Our study found trait anxiety and trait depression were most predictive of increased preoperative psychological stress (dysphoria) on the day of surgery, not PTSD. Although the primary outcome variable in McGuire's[7] study (ED) was fundamentally different than dysphoria, both studies utilized similar psychological instruments to measure anxiety, depression, and PTSD symptoms, and both studies conducted similar statistical modeling. Taken together, these findings counter the commonly held assumption by many anesthetists that PTSD suggests increased preoperative stress or risk for postoperative ED. Again, these two studies emphasize how multifactorial perioperative phenomena may be and that no one emotion or behavior is necessarily absolute in determining an individual's perioperative stress response.

Our study found anxiety measured days prior to surgery was not significantly associated with increased negative emotions (dysphoria) on the day of surgery. Instead, higher degrees of depression were most predictive of increased negative emotions in all subjects, particularly in combat-exposed veterans. In addition, combat exposure alone significantly contributed to increased preoperative dysphoria on the day of surgery when controlling for anxiety, depression, and PTSD. These findings corroborate anecdotal accounts by military anesthetists reporting combat veterans appear more stressed perioperatively; however, depression contributing to increased dysphoria is a new finding. One reason for this new finding might be the underreporting or lack of measurement of depression in previous preoperative stress literature. Another explanation could be combat-exposed individuals have an overall negative perception of the perioperative experience, ultimately manifesting in depressive-like symptoms. Clinically speaking, these findings may encourage anesthesia providers to reconsider other mental health disorders in combat veterans presenting for surgery rather than to assume that PTSD is the only telltale sign whether a patient will exhibit more stress-related behaviors perioperatively.

The VAS-stress was another measure used to determine the preoperative psychological stress response. This measure allowed investigators to gauge an individual's perception of stress as he or she progressed through the preoperative period. Two levels of subjective stress were computed for analysis; i.e., *mean* and *peak* VAS-stress values. When all study subjects were included in an analysis using VAS-stress *mean* values as the outcome variable, trait anxiety and trait depression (PHQ-4) were the only predictor variables significantly contributing to subjective stress on the day of surgery. When considering VAS-stress *peak* values, trait anxiety and trait depression were again the only variables significantly contributing to subjective stress. Statistically speaking, a trend emerged throughout this study related to trait measures of anxiety and depression and the preoperative psychological stress response. Therefore, other mental health disorders, such as depression or anxiety, may have more predictive value in anticipating a combat veterans' perioperative stress response than PTSD alone.

Another study aim was to explore the physiological stress response using a noninvasive surrogate of the sympathetic nervous system, in this case SAA. Each of the statistical models exploring SAA total output, as well as *mean* increase values, were not found to be statistically significant. Interestingly, SAA *mean* values in the NCE group were slightly higher at each time point as compared to the CE group, and although not statistically significant, this was an unexpected finding. One explanation are individuals with prior combat exposure or a history of mental illness may not be as physiologically "ramped up," or may be less responsive physiologically when encountering stressful situations.[19] This may be best represented by the results from the SAA *peak* value analysis. These results indicated that although 6% of the variability in SAA *peak* values was explained by the predictor variable combat exposure (WRAIR-CES), this was a negative relationship; suggesting that individuals with more combat experience produced less SAA and individuals with less combat experience produced more SAA.

Effect of Problems or Obstacles on the Results

A concern throughout the study was the participant's response when completing the instruments measuring anxiety, depression, and PTSD symptoms. Because of concern and sensitivity related to mental health disorders like PTSD or depression, the PI was directed by Naval Medical Center San Diego's Institutional Review Board to consult the Mental Health Department (MHD) at NHCP if individuals indicated a potential caseness or diagnosis of anxiety, depression, or PTSD following the completion of the study instruments. As a result, the PI informed individuals during the consenting process that a referral to the MHD would be completed if study instruments suggested a potential diagnosis. Ultimately, this may have resulted in some subjects underrating or minimizing mental health symptoms to avoid a MHD consult or diagnosis. In addition, many participants expressed concern about a potential diagnosis of PTSD or depression, suggesting a mental health disorder could affect their career in a negative manner. Despite this potential problem, the PI ensured all subjects were informed about instrument scoring, mental health referrals, and potential diagnoses.

One obstacle that may have significantly affected SAA results was operating room (OR) scheduling. Prior to initiating the study, the PI met with NHCP OR schedulers to discuss SAA diurnal patterns and the necessity to schedule a subject's surgery as the first surgical case in the morning (i.e., 0730). However, the ability to coordinate a specific surgical start time proved to be extremely difficult due to the dynamic nature of an OR. For example, some study subjects underwent surgery later in the day due to emergency surgeries, while other surgeries were delayed because of surgeon preference or military-related training. As a result, many surgeries began mid-morning to early afternoon, which resulted in SAA production being potentially elevated since SAA increases throughout the day. Because of this issue, the PI would recommend future investigators consider biomarkers less affected by time or diurnal patterns.

One additional concern, and potential confounding variable, was NHCP's transition into a new facility on Camp Pendleton. Some subjects consented to participate in the study at the *old* facility, but underwent surgery in the new hospital; hence, the new facility may have created perceived barriers or stressors not apparent or even relevant prior to the move. However, a limited number (i.e., < 10) of subjects enrolled in the study at the old facility and had surgery in the new hospital.

Limitations

This study had several limitations; one being the study was conducted at a military hospital located on a U.S. Marine Corps installation, predominately resulting in U.S. male Marines enrolling in the study. A broader spectrum of patients from other U.S. military services, in addition to a larger sample size including more females, would be necessary to validate this study's findings.

As already mentioned, it was difficult to manage the diurnal pattern known to exist with SAA. The investigator attempted to coordinate each subject's surgical time on the day of surgery; however, this proved to be too difficult for many reasons not easily managed by OR schedulers. In addition, the variability in time between SAA sampling (i.e., times between TP-1 and TP-2, etc.) was very difficult to manage, thus further complicating the interpretation of the study data.

Another potential study limitation was individual thermal comfort. In a study using similar methodology and study variables, Spence et al[20] reported subjects feeling colder on the day surgery exhibited a greater SAA response. In addition, other research suggests extremes in temperature may significantly affect SAA responsiveness.[21] Future investigations exploring perioperative stress in military personnel, or combat veterans, would most likely benefit from the measurement of thermal comfort, particularly if biomarkers have potential to be impacted by temperature.

An additional limitation were instruments used to assess anxiety and depression relative to those used by other military researchers measuring similar constructs. For example, McGuire[7] conducted a study at NHCP exploring postoperative ED and used the State-Trait Inventory to measure anxiety and the PHQ-9 to measure depression.[9] Our investigation utilized an abbreviated instrument (PHQ-4) to measure anxiety and depression in order to minimize instrument burden; hence, the PHQ-4 exhibits high reliability and validity. Regardless, it is noteworthy to suggest that military researchers develop or agree upon a battery of instruments to measure frequently utilized constructs in future investigations.

Conclusion

The aim of this investigation was to determine the preoperative psychological and physiological stress response in military personnel with varying degrees of combat exposure. Questions remain how combat experience affects an individual's perception and/or reaction to stressors encountered perioperatively. Anecdotally speaking, military anesthetists perceive combat veterans to be more prone to exhibiting a heightened perioperative stress response, particularly individuals with a history of PTSD. The first aim in our study explored predictive relationships between the psychological stress response while controlling for anxiety, depression, PTSD, and combat exposure. Results from this investigation found trait depression and combat exposure explained approximately 23% of negative emotions, specifically dysphoria, on the day of surgery. This investigation also found combat exposure explained an additional 5% of negative emotions on the day of surgery, a finding not reported in current perioperative stress literature. In addition, findings from this study suggest PTSD may not be as significant or influential when predicting an individual's preoperative stress response. This finding is especially important considering this is the second study to suggest PTSD may not be a reliable predictor of perioperative stress.

In regards to this study's second aim, no predictive relationships were identified between the predictor variables and the preoperative physiological stress response. The inability to control for SAA diurnal patterns because of difficult OR scheduling could have profoundly influenced a subject's SAA production, especially if a surgery did not take place until late afternoon. Therefore, measures of physiological stress in future preoperative stress research should consider biomarkers less effected by diurnal patterns or other metabolic disturbances.

Lastly, most perioperative stress-related literature describes preoperative stress in terms of anxiety; however, there is little understanding related to other emotions or mental health disorders, such as trait depression and PTSD and their relationship to perioperative stress. This study corroborated what many military perianesthesia clinicians have witnessed, that being combat veterans exhibit more negative emotions preoperatively. However, additional research is necessary to validate this study's findings.

Significance of Study Results to Military Nursing

This is the first study known to this author to measure the *pre*operative stress response in military members with varying degrees of combat exposure. Minimal research exists exploring combat exposure and its potential influence upon the perioperative stress response. The new knowledge from this study includes relationships between trait depression, combat exposure, and increased negative emotions on the day of surgery. There is a well-established relationship between mental health disturbances or disorders and combat exposure; however, this may be the only investigation to study the preoperative stress response in military personnel while accounting for combat experience(s). This has significant military nursing implications in that many perianesthesia providers assumed PTSD as the primary cause of perioperative-related behaviors in combat veterans; however, this study suggests trait depression may contribute significantly more to increased preoperative dysphoria.

Our research also identified a relationship found in another study measuring similar psychological measures in combat veterans perioperatively. McGuire[7] found trait and state anxiety contributed significantly to postoperative ED in individuals reporting prior combat experience; however, PTSD was not predictive of postoperative ED. Likewise, our investigation found PTSD to be the least predictive of all variables when considering negative emotions on the day of surgery. Therefore, clinicians should consider other mental health disorders, such as anxiety or depression, when planning or caring for combat veterans perioperatively.

This study is also relevant to military nursing in that it provided additional perioperative stress-related research necessary to support future investigations in the military. In addition, this study employed psychological instruments previously used other military nurse researchers, thus providing the ability to compare and contrast study findings. Taken together, it supplements groundwork already completed by nurse scientist(s) to foster the interpretation and understanding related to perioperative stress phenomena.

Changes in Clinical Practice, Leadership, Management, Education, Policy, and/or Military Doctrine that Resulted from Study or Project

Despite findings identified throughout this study, no clinical, policy, or administrative change(s) have been realized to date. However, this study was significant in that it corroborated reports by military anesthetists that combat veterans appear more stressed preoperatively. Furthermore, this investigation identified other mental health disorders that may be contributing to preoperative stress more than PTSD alone. Most importantly, however, our study significantly furthered the understanding of preoperative stress in combat veterans.

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Summary of Dissemination

Type of Dissemination	Citation	Date and Source of Approval for Public Release
Publications in Press	Manuscript currently being developed discussing study findings related to predictive relationships between preoperative dysphoria, combat exposure, and trait depression.	Not submitted for approval
Poster Presentations	● Bopp E, Burkard J, Ryan M, Spence D, Wright D, "Is Combat Exposure Predictive of Higher Preoperative Stress in Military Members?" Academic Research Competition, First Place, Resident Category, Naval Medical Center San Diego, San Diego, CA, April 2014, sponsored by Naval Medical Center San Diego. ● Bopp E, Burkard J, Ryan M, Spence D, Wright D, "Is Combat Exposure Predictive of Higher Preoperative Stress in Military Members?" Navy-Wide Academic Research Competition, First Place, Resident Category, Naval Medical Center Portsmouth, Portsmouth VA, May 2014, sponsored by Naval Medical Center Portsmouth. ● Bopp E, Burkard J, Ryan M, Spence D, Wright D, "Is Combat Exposure Predictive of Higher Preoperative Stress in Military Members?" TriService Nursing Research Program's Research and EBP Dissemination Course, Keynote Speaker, San Antonio, TX, September 2014, sponsored and funded by TriService Nursing Program.	8/6/2014 External Affairs, USUHS; 9/4/2014 External Affairs, USUHS

Reportable Outcomes

Reportable Outcome	Detailed Description
Applied for Patent	None
Issued a Patent	None
Developed a cell line	None
Developed a tissue or serum repository	None
Developed a data registry	None

Recruitment and Retention Table

Recruitment and Retention Aspect	Number
Subjects Projected in Grant Application	120
Subjects Available	Active duty members scheduled for elective surgery at NHCP
Subjects Contacted or Reached by Approved Recruitment Method	See below[1]
Subjects Screened	See below[1]
Subjects Ineligible	See below[1]
Subjects Refused	See below[1]
Human Subjects Consented	120
Subjects Who Withdrew	1
Subjects Who Completed Study	119
Subjects With Complete Data	107
Subjects with Incomplete Data	12

[1]Patient enrollment took place in the SDSU at NHCP. After preoperative screening by SDSU staff, the PI was introduced to the patient and a brief description of Project N12-P16 was provided. If the patient verbalized an interest in participating in the study, then the PI escorted the patient to an adjacent room for full disclosure of the study; hence, the PI only maintained a record/study log on patients actively enrolled in Project N12-P16.

Demographic Characteristics of the Sample

Characteristic	
Age (yrs)	27.28 ± 6.23
Women, n (%)	8 (7%)
Race	
White, n (%)	78 (65.5%)
Black, n (%)	9 (7.6%)
Hispanic or Latino, n (%)	23 (19.3%)
Native American, n (%)	3 (2.5%)
Asian, n (%)	4 (3.4%)
Other, n (%)	2 (1.7)
Military Service or Civilian	
Air Force, n (%)	0
Army, n (%)	1 (<1%)
Marine, n (%)	105 (88%)
Navy, n (%)	13 (11%)
Civilian, n (%)	NA
Service Component	
Active Duty, n (%)	120 (100%)
Reserve, n (%)	NA
National Guard, n (%)	NA
Retired Military, n (%)	NA
Prior Military but not Retired, n (%)	NA
Military Dependent, n (%)	NA
Civilian, n (%)	NA

Final Budget Report

Final Invoice

Grant Number: HT9404-12-1-TS16
N12-P16

PI Name: Eric Bopp

Grant Title: Is Combat Exposure Predictive of Higher Preoperative Stress in Military Members?

Reporting Period: 1 August 2012 to 31 Oct 2014

Category		Award Amount	Current Expenditures	Previously Reported	Variance
Personnel		$ -	$	$	$
Consultant		$	$ -	$ -	$ -
Equipment		$ -	$	$ -	$
Supplies		$ 10,857.00	$ -	$ 7,085.79	$ 3,771.21
Travel		$ 1,822.00	$ 939.20	$	$ 882.80
Patient Care Costs		$	$	$	$
Other		$ 1,325.00	$ (9.21)	$ 359.20	$ 975.01
Consortium/ Contractual Costs	Direct	$ -	$	$	$
	Indirect	$ -	$	$	$
TOTAL		$ 14,004.00	$ 929.99	$ 7,444.99	$ 5,629.02

MPreciado

University of San Diego Authorized Representative Signature

MARIA G PRECIADO, ACCOUNTING MANAGER

University of San Diego Authorized Representative Printed Name & Title

E. B

PI Signature